The effects of short-term dietary calorie restriction combined with aerobic exercise on systemic inflammation in overweight or obese individuals with knee osteoarthritis: a randomised controlled trial

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Abstract

Purpose:

The purpose of this study is to determine the effects of 4-weeks dietary calorie restriction alone (CR) compared to CR with aerobic exercise (CR+E) on systemic inflammation and index knee pain in overweight and obese individuals with knee osteoarthritis (OA).

Methods:

Twenty-three individuals with knee OA completed a randomised controlled trial. Participants in the CR group (n=9, BMI: 30.0 ± 2.4 kg/m^2, 56 ± 5 years) were asked to reduce their habitual energy intake by 5000 kcal/week for 4 weeks, and those randomised to the CR+E group (n=14, BMI: 32.3 ± 4.8 kg/m^2, 57 ± 5 years) were asked to follow the same dietary CR and perform five, 30-minute bouts of moderate intensity cycling per week. Blood markers of inflammation, body composition, function, and pain were compared after a 4-week intervention period by ANCOVA, using pre-intervention value as a covariate.

Results:

There was no difference in CRP between groups at post-intervention (p=0.517, d=0.31). IL-6 was lower (p<0.01; d=1.69) at post-intervention in the CR+E group (1.36 mg/dL, 0.72 to 2.00) compared to CR group (2.98 mg/dL, 2.22 to 3.73). Visual analogue scale (VAS) knee pain was lower (p<0.01; d=1.29) at post-intervention in the CR+E group (2, 1 to 3) compared to the CR group (4, 3 to 5). The time to complete the stair climb test was lower at post-intervention in the CR+E group compared to the CR group (p=0.016, *d*=1.17).

Conclusions:

Four weeks of moderate-intensity aerobic exercise training combined with CR led to a greater reduction in IL-6, but not CRP, compared to CR alone. The addition of exercise to CR led to greater reduction in knee pain compared to CR alone.

Trial Registration

ClinicalTrials.gov (ID: NCT05518890).

Introduction

Knee osteoarthritis (OA) is considered one of the leading causes of chronic disability worldwide (1) and its prevalence has doubled in the last 30 years (2). Previously regarded as a wear and tear disease, research now shows that low-grade, chronic inflammation plays a key role in knee OA progression (3, 4).

Radiography is used for the diagnosis and monitoring of disease progression in knee OA, but only provides a limited representation of disease activity and modestly correlates with pain and functional improvement, with many individuals with clinically significant symptoms presenting minimal or no radiographic change (5). This disconnect highlights that OA progression can be driven by systemic metabolic, inflammatory and biomechanical processes that cannot be captured by imaging (6). Additionally, knee OA is now understood to consist of distinct phenotypes that may respond differently to conservative interventions (7, 8). Imaging cannot differentiate between phenotypes, nor can they detect short-term changes in systemic inflammation that conservative interventions target (9). Biomarkers offer a more sensitive means of detecting biological effects within weeks rather than years (10)(REF). Integrating biomarker assessment into knee OA trials can enhance mechanistic understanding, improve prediction of treatment response, and support the development of more personalised, phenotype-specific management strategies.

The most influential and comprehensively studied group of biomarkers associated with the inflammatory pathogenesis of knee OA are well known but not limited to, C-reactive protein (CRP), interleukin (IL)-6, tumour necrosis factor (TNF)-α, IL-1β, IL-4, IL-10, and IL-13. CRP is arguably the most researched inflammatory marker in knee OA and

has been shown to decrease cartilage volume loss, delay disease progression (11) and improve local joint inflammation (12). In addition to being associated with the physiological disease progression, various biomarkers (e.g., CRP, IL-6, TNF-α and IL-1β) have also been associated with clinical outcomes of pain, function and quality of life (QoL). A long term cohort study(13) reported that both baseline, and change in CRP over 5 years is positively associated with changes in total knee pain, pain at night, and pain whilst sitting/lying – as reported using the Western Ontario and McMaster Universities Arthritis (WOMAC) Index (14). Besides improvements in pain, lower CRP levels have been associated with improvements in QoL post-surgery (15). TNF-α, IL-1β and IL-6 have been positively associated with pain, stiffness, and physical function (16, 17). As well as those pro-inflammatory biomarkers that are associated with disease progression, cartilage degeneration and clinical symptoms, it is also important to highlight the anti-inflammatory biomarkers (i.e., IL-4, IL-10 and IL-13), that are associated with cartilage repair which can act to suppress and/or inhibit MMP-13 expression through the suppression of TNF-α and IL-1β (18, 19).

Weight loss and exercise are the first line of conservative treatment recommended for the management of knee OA (20). Long term weight loss studies, involving diet and exercise manipulation have demonstrated beneficial effects on systemic inflammation and clinical outcomes (i.e., pain, function and quality of life) in individuals with knee OA living with overweight or obesity (9). Despite this, the current evidence on the effects of diet alone, and diet combined with exercise treatments on a broad array of systemic inflammatory biomarkers in this population remains weak (21) and there is a need for short-term interventions (i.e., ≤ 4 weeks) in order to determine whether improvements in systemic inflammation and clinical outcomes can be achieved in the short-term.

The objective of this study was to determine the effects of 4-weeks of dietary calorie restriction alone (CR) or combined with aerobic exercise (CR+E) on systemic inflammation in individuals with knee OA living with overweight or obesity. The primary hypothesis was that CRP will be reduced to a greater extent in the CR+E group, compared with the CR only group.

Methods

Study population

Males and post-menopausal females aged between 45 and 69 years old were recruited for the study. Participants were invited to an initial screening visit if they had a clinical diagnosis of uni- or bi-lateral knee OA and a self-reported body mass index (BMI) between 27.5 and 40 kg/m^2. Additionally, individuals completed the Oxford Knee Score (OKS) (22) to assess severity of knee OA, with individuals scoring between ≥20 to ≤35 for the index knee invited to in-person screening visit. This range was chosen to recruit individuals with mild-to-moderate of moderate symptoms, who are typically viewed as appropriate candidates for non-surgical, conversative OA management, including diet and exercise. Exclusion criteria included those with; a resting blood pressure >180/120 mmHg, any knee/hip related surgery within the last 12 months, current smokers (or those who had quit <6 months prior), or a current metabolic disease.

Study design and protocol

This randomised control trial was approved by the Southwest National Research Ethics Committee (REC reference: 20/SW/0063) and registered on ClinicalTrials.gov (ID: NCT05518890). Recruitment commenced from January 2022 and all follow ups completed by March 2023. Participants were primarily recruited from a healthcare clinic (Virgin Care) for individuals diagnosed with knee OA, and through local

community advertisement. Informed written consent was obtained from all participants prior to testing. Participants attended the laboratory at the University of Bath on four separate occasions. During the first visit, participants were re-screened for eligibility (resting blood pressure <180/120 mmHg, height and weight measured) and were asked to wear a physical activity monitor and record a food diary for seven consecutive days to determine PAL and energy intake, respectively. Participants with a daily physical activity (PAL) >2.00 were excluded at this point. Visits two (baseline), three (pre-intervention) and four (post-intervention) were separated by 4-weeks, with a control period between visits two and three, allowing participants to act as their own controls (23). Between visits three and four, participants were randomised to an intervention; either CR or CR+E. Randomisation was performed by an independent researcher using a minimisation approach, with groups balanced for key characteristics (sex, age, BMI, and OKS) at baseline, with factors equally weighted and no random elements. All outcomes were measured at visit two and repeated at visits three and four. The research team and participants were not blinded to group assignments following the randomised allocation.

Pre-trial standardisation procedures

Participants were required to record their weighed food intake in the 24 hours before visit two (baseline) to replicate their diet in the 24 hours before visit three (pre-intervention) and visit four (post-intervention). Participants were also asked to avoid caffeine, alcohol, and strenuous exercise for 24 hours before each trial visit and arrive at the laboratory in a fasted state (>10 hours).

Dietary calorie restriction (CR Group)

For the 4-week intervention period, participants in the CR group, reduced their habitual energy intake by 5000 kcal per week, prescribed individually based on their 7-day food

diary and physical activity monitoring (i.e., energy intake and energy expenditure). The dietary restriction was based on an absolute energy deficit achieved by the intake of smaller food portions, which was calculated by subtracting from their energy expenditure (Actiheart^{TM}) rather than energy intake to avoid issues with participants' under-reporting food intake (24). The energy deficit was induced by multiplying the weight of all individual foods from the 7-day diary by an individual factor gathered from the energy expenditure data, allowing the desired energy intake for the intervention period to be determined (25). Participants were advised how many calories to aim to eat per day to achieve the 5000 kcal/week deficit and recommended to use a publicly available calorie tracker (e.g., MyFitnessPal).

Dietary calorie restriction, combined with exercise (CR+E Group)

For the 4-week intervention period, as per the CR group, participants in the CR+E group reduced their habitual energy intake by 5000 kcal per week. Additionally, participants were asked to perform five, 30-minute aerobic exercise sessions per week, at home on a standardised portable cycle ergometers provided by the research team (DKN AM-E, DKN Technology, Belgium). The intensity of each exercise session was based upon individuals' perception, using the original rating of perceived exertion (RPE) scale of 6-20 (26). The target intensity was progressively increased throughout the exercise intervention (i.e. week 1: RPE 12, week 2: RPE 13, week 3: RPE 14, week 4: RPE 15). These target intensities span the range from moderate-intensity exercise to the lower boundary of vigorous-intensity exercise(27). Heart rate (HR) was measured and tracked during each exercise session (Polar A300, Polar Electro, Finland). Participants were asked to record average and maximum HR from each exercise session in a diary to track adherence and progression.

Outcome measures

Body Composition

Body mass was measured to the nearest 0.1 kg (BRW1000; Decto, Webb City, MO, USA). Dual-energy X-ray absorptiometry (DEXA) (Discovery; Hologic, Bedford, UK) was used for the assessment of body composition, with participants positioned in the middle of the scanning table with feet spaced evenly each side of the mid-point of the body and arms placed mid-prone with an equal gap to the trunk. Waist and hip circumference were measured using a non-metallic tape measure to the nearest 0.5 cm. Waist circumference was measured at the end of normal expiration, at the mid-way point between the lowest palpable rib and the iliac crest; and hip circumference was measured at the widest part of the buttocks.

Blood Measurements

Blood samples (20 mL) were collected in the fasted state via venepuncture from the median cubital and cephalic veins. Whole blood was placed in serum separation tubes and left to stand at room temperature for 15 min before centrifugation. For plasma, whole blood was placed in tubes coated with EDTA and centrifuged immediately. Samples were centrifuged at 4000 g for 10 min at 4°C. Aliquots were immediately cooled on dry-ice, being stored in -80°C freezer for long-term storage.

Plasma and serum samples were thawed at room temperature prior to analysis and prepared according to the manufacturer instructions. Serum high-sensitivity (hs) CRP (mg/L) was measured on an automated analyser (Randox RX Daytona+; Randox Laboratories, Antrim, UK). Pro- and anti-inflammatory cytokines (IL-6, IL-1β, TNF-α, IL-17a, IL-18, IL-8, IL-10, IL-4, IL-13, IL-1RA) were analysed using multi-array technology, combining arrays and electrochemiluminescence, a light emission process whereby light is emitted when analytes are identified in a sample, enabling

precise quantitation of multiple analytes in a single sample (MESO QuickPlex SQ 120MM, MSD, Maryland, USA). A 5-fold dilution factor was used to ensure that all analytes within the multiplex assay were within the standard curve. All intra-assay coefficients of variation were ≤10%. Markers of metabolic health (glucose, triglycerides, non-esterified fatty acids (NEFA), high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, and total cholesterol) were measured on an automated analyser via turbidimetry (Randox RX Daytona+, Antrim, UK) using commercially available immunoassays (Randox Laboratories, Antrim, UK). All samples for each participant were completed on the same multiplex or automated run.

Pain and Self-Report Health Status

Participants verbally reported their resting symptomatic pain in their index knee, on a 0-10 visual analogue scale (VAS) (where 0 indicated no pain and 10 indicated worst pain imaginable) (28). Participants also completed three questionnaires related to their condition and general health status; i) the Knee Injury and Osteoarthritis Score (KOOS) (29); ii) the short form-36 health survey (SF-36) (30), and iii) the EQ-5D-5L(31).

Functional Tests

Participants completed a set of functional tests as recommended by the Osteoarthritis Research Society International (OARSI) (32), which included: i) a 30-s chair stand test, ii) a 40-m fast paced walk test, iii), a stair climb test, and iv) a timed up and go test.

Statistical analysis and sample size

All statistical tests were performed using SPSS v29 (IMB, USA). All data were normally distributed determined by visual inspection of residual plots. The final analyses were based on a per-protocol principle, where participants in the CR+E group must have completed at least 75% (15 of 20) of their exercise sessions to be included in the subsequent analyses. Paired t-tests were performed from baseline to pre-intervention to determine the stability of inflammatory markers and the VAS score. ANCOVA was used to assess the differences between groups at post-intervention, with pre-intervention values as the covariate. Participants with missing data points were removed from corresponding analysis only, and no data points were imputed. Effect sizes (Cohen's *d*) were calculated for all variables, and interpreted as: small effect, 0.20–0.50; medium effect, 0.50–0.79; and large effect, ≥0.80. All in text values are reported as mean ± SD, unless stated otherwise. Statistical significance was set at $P \leq 0.05$.

An a priori power calculation was based upon a previous RCT (25), which reported reduction in hsCRP (effect size $d=1.22$) following 3 weeks of energy restriction (5000 kcal/week) and vigorous intensity exercise (5 sessions/week) in overweight, but otherwise healthy participants. We hypothesised that the effect of the CR intervention would be smaller, due to smaller energy restriction and independent impact of exercise training upon CRP. Therefore, we anticipated a reduction in CRP (primary outcome) following CR combined with exercise equivalent to an effect size of 0.85. With an $\alpha=0.05$ and $\beta=0.80$, *a* priori calculation determined that we would require a total of 13 participants per intervention group, excluding dropouts.

Results

Thirty participants agreed to take part, and three of these participants were deemed not eligible during the initial screening visit. Four participants withdrew from the study (Figure 1), equating to a drop-out rate of ~15% (4/27). Therefore, 23 participants (Table 1) completed baseline, pre-intervention and post-intervention assessments and were therefore included in the final analysis.

[TABLE 1 INSERT HERE]

In the CR+E group, 11 participants completed all exercise sessions (20/20), 2 participants missed one exercise session (19/20), and one participant missed three exercise sessions (17/20). The average HR for Weeks 1-4 of the exercise sessions were 105 ± 17 bpm, 110 ± 18 bpm, 114 ± 19 bpm, and 117 ± 19 bpm respectively. At baseline, self-reported energy intake was 1904 ± 496 kcal/day and 1951 ± 317 kcal/day for the CR and CR+E groups respectively (p=0.459). During the intervention, self-reported energy intake was 1423 ± 350 kcal/day and 1360 ± 411 kcal/day for the CR and CR+E groups respectively. The decrease in body mass (3.9 ± 1.2 kg) for the CR+E group was greater than the CR group (1.9 ± 2.7 kg; p=0.043; Table 3). There were no other differences in body composition metrics between groups (Table 3).

[FIGURE 1 INSERT HERE]

[FIGURE 2 INSERT HERE]

Blood samples were obtained for 8/9 participants in the CR group and 13/14 participants in the CR+E group. There were differences between baseline and pre-intervention values for IL-17A (p=0.036), IL-8 (p<0.01), IL-1β (p=0.050), and IL-1RA (p=0.023) (data not shown). Body mass was greater (0.5 ± 1.0 kg) at pre-intervention compared to baseline (p=0.043). There were no other differences between baseline and pre-intervention values for any metabolic health marker, body composition metric, functional assessment score, or self-reported measure (data not shown).

There was no difference in CRP between CR (n=8) and CR+E (n=13) at post-intervention (p=0.517, d=0.31; Figure 2). IL-6 was lower at post-intervention in the CR+E group (n=11) compared to the CR group (n=8) (p<0.01, *d*=1.69; Figure 3). There were no other differences in inflammatory markers between groups at post-intervention (Table 3). VAS was lower at post-intervention in the CR+E group compared to the CR group (p<0.01; *d*=1.29; Figure 4). There were no differences in any blood markers of metabolic health between groups at post-intervention (Table 2).

The time to complete the stair climb test was lower at post-intervention in the CR+E group compared to the CR group (p=0.016, *d*=1.17; Figure 5). There were no differences between groups for timed up and go (p=0.147), 40-m walk speed (p=0.068), and chair stand (p=0.168) (Figure 5).

Pain and knee-related quality of life subscale scores from the KOOS were improved in the CR+E group compared to the CR group at post-intervention (both p=0.018; Table

5). The sport and recreation subscale of the KOOS was not included in the final analysis due to a low proportion of participants completing these questions.

Physical functioning, physical health, emotional problems, energy/fatigue, emotional wellbeing, pain, and general health subscale scores from the SF-36 were improved in the CR+E group compared to the CR group at post-intervention (Table 5). There were no differences in subscales of the EQ-5D between groups at post-intervention (all $p>0.271$; data not shown).

[TABLE 2 INSERT HERE]

[FIGURE 3 INSERT HERE]

[FIGURE 4 INSERT HERE]

Discussion

The aim of this study was to compare the effects of dietary calorie restriction alone or in combination with aerobic exercise, on systemic inflammatory biomarkers and pain associated with knee OA. To our knowledge, this is the first short-term intervention study that has compared CR+E and CR only in the knee OA population. There was no difference between groups at post-intervention for the CRP, the primary outcome. However, IL-6, a pro-inflammatory cytokine, was lower following CR+E compared to CR only. Further, index knee pain was lower following CR+E compared to CR only.

There are limited data available in this population to compare our results with, and of those that are available, the quality is generally poor (21). Although reductions in CRP have been reported following short-term diet and exercise interventions in otherwise healthy obese populations (25), the inflammatory profile of knee OA may differ. In a knee OA population, meaningful decreases in CRP have most consistently been observed in interventions of a longer duration. For example an 18-month diet and

exercise intervention (33) produced significant reductions in CRP levels, but pre-intervention values (8.8 ± 11.3 mg/L) were notably higher than in our study (2.8 ± 0.6 mg/L), providing a larger physiological range for improvement. Taken together, these factors suggest that the absence of a CRP reduction in our study may be representative of the expected temporal dynamics of systemic inflammation. Shorter-term interventions may be insufficient to elicit measurable changes in CRP, especially when baseline levels are lower. This highlights that CRP is unlikely to serve as a sensitive short-term biomarker of response to diet and exercise treatment in knee OA, even when other clinical or biological improvements are observed.

Whilst there were no differences for a range of pro-inflammatory markers, IL-6 was lower following CR+E (1.36 ± 0.64 mg/dL) compared to CR only (2.98 ± 0.76 mg/dL). The IDEA trial (9) found that a combination of CR+E and CR only were both effective in reducing basal concentrations of IL-6 over an 18 month intervention period, but we have shown that a short-term intervention of CR+E can also significantly reduce basal concentrations of IL-6, whilst short term dietary energy restriction may be less effective. Systemic IL-6 concentrations are positively associated with obesity (34), and so the larger reduction in body mass seen in the CR+E group may explain the larger reduction of IL-6. IL-6 has also been shown to decrease after only 4-weeks of moderate intensity aerobic exercise (35), suggesting that exercise energy expenditure alone could be the influencing factor on the reductions seen in IL-6 in the CR+E group.

Symptomatic pain was lower at post-intervention in the CR+E group (Δ -1.6 ± 2.1) in comparison to the CR only group (Δ -0.6 ± 1.2). The minimal clinically important difference (MCID) for VAS pain in the knee OA population is accepted to be 19.9 mm on a 0-100 VAS (36), translating to approximately 2 on a 0-10 scale, as utilised in this study. This reduction in VAS pain for CR+E group, paired with the subjective and

290 individualised nature of pain, represents a promising reduction. The greater reduction
291 in body mass in the CR+E (-3.9 ± 1.2 kg) compared with the CR only group (-1.9 ± 2.7
292 kg) could explain the greater reduction in symptomatic pain, with previous research
293 highlighting the dose response relationship between weight loss and pain in individuals
294 with knee OA (37). Additional potential mechanisms that could explain the greater
295 reduction in pain in the CR+E group could be linked to the effects of exercise. For
296 example, an increase in upper leg strength, a reduction in extension impairments and
297 improvements to proprioception (38).

298 The addition of moderate intensity cycling to the CR improved time to complete stair
299 climb test, and a range of quality-of-life metrics. These findings are in line with the
300 ADAPT trial (39) which reported combined exercise and diet-induced weight loss
301 across 18-months resulted in the greatest improvement in 6-minute walk test distance
302 and stair climb time, compared to other lifestyle interventions, including diet-induced
303 weight loss only. Despite performance metrics of other functional outcomes appearing
304 to approach statistical significance (e.g., 40-m walk test), there were no other
305 differences between groups. However, the CR+E group reported many improvements
306 in SF-36 and KOOS subscales, including physical functioning, physical health, and
307 ability to perform activities of daily living, compared to CR only. This supports the role
308 of exercise in improving physical function and health-related quality of life in individuals
309 with knee OA (40).

310 **Limitations**

311 Firstly, we did not reach the *a* priori sample size calculation in each group, with four
312 dropouts in the CR group, resulting in an imbalance between groups (CR: 9; CR+E:
313 14). The effect size between groups for CRP was small (d=0.31), but nonetheless, this
314 is a substantial limitation of the study and therefore results should be regarded as

preliminary rather than confirmatory. Additionally, this may have limited our ability to detect significant differences in outcomes which approached statistical significance (e.g., 40 m walk test). Secondly, participants adherence to the calorie restriction should be considered. Only, ten participants met or exceeded the 5000 kcal/week deficit. Whilst it was not feasible to request participants to log their food for the entire four-week intervention period, a better method may have been to check in with participants after their first week of food logging to discuss any challenges or difficulties they were experiencing trying to adhere to the prescribed caloric deficit.

Conclusion

To conclude, while a short-term combined calorie restriction and aerobic exercise intervention did not reduce CRP concentrations, it led to significant reductions in circulating IL-6 concentrations in individuals with knee OA who were obese and/or overweight, compared with dietary calorie restriction only. The decrease in VAS pain was greater in the combined calorie restriction and aerobic exercise group compared with the calorie restriction only. This may be related to the reduction in IL-6 seen in the calorie restriction combined with aerobic exercise group and the greater decrease in body mass. These results combined suggest that the prescription of exercise in line with the general population physical activity guidelines (≥150 minutes of moderate-intensity aerobic exercise per week) (41), which have also been determined as appropriate for people with knee OA (42), paired with a 5000 kcal/week dietary calorie restriction may be utilised by clinicians and other healthcare professionals to reduce systemic inflammation and reduce knee pain, at least in the short-term.

List of Abbreviations

OA *osteoarthritis*

CRP *C-reactive protein*

IL *interleukin*

TNF *tumor necrosis factor*

MMP *matrix metallopeptidase*

CR *calorie restriction*

CR+E *calorie restriction combined with aerobic exercise*

OKS *Oxford Knee score*

BMI *body mass index*

PAL physical activity level

RPE rating of perceived exertion

HR *heart rate*

NEFA *non-esterified fatty acids*

LDL *low-density lipoprotein*

HDL *high-density lipoprotein*

VAS *visual analogue scale*

SD *standard deviation*

ANCOVA *analysis of covariance*

MCID *minimal clinically importance difference*

WOMAC *Western Ontario and McMaster Universities Osteoarthritis Index*

Declarations

Ethics approval and consent to participate

This randomised control trial was approved by the Southwest National Research Ethics Committee (REC reference: 20/SW/0063) and registered on ClinicalTrials.gov (ID: NCT05518890).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This work was partly supported by the ** as part of a PhD project.

Acknowledgements

The authors would like to extend their acknowledgement and gratitude to the participants who took part in this RCT.

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Figure legends

Figure 1. CONSORT study flow diagram

Figure 2. CRP at pre-intervention and post-intervention for calorie restriction (n=8) and calorie restriction combined with aerobic exercise (n=13) groups. Data presented is mean and 95% CI.

Figure 3. VAS at pre-intervention and post-intervention for calorie restriction (n=9) and calorie restriction combined with aerobic exercise (n=14) groups. Data presented is mean and 95% CI.

Figure 4. IL-6 at pre-intervention and post-intervention for calorie restriction (n=8) and calorie restriction combined with aerobic exercise (n=11) groups. Data presented is mean and 95% CI.

Figure 5. Functional tests (stair climb, timed up and go, 40-m walk speed, and chair stand) at pre-intervention and post-intervention for calorie restriction and calorie restriction combined with aerobic exercise groups. Data presented in mean and 95% CI.

Table 1. Participant characteristics (n=23)

	Calorie Restriction	Calorie Restriction + Exercise
n	9	14
Age (yrs)	56 ± 5	57 ± 5
Sex		
Males	3	5
Females	6	9
BMI	30.0 ± 2.4	32.3 ± 4.8
Disease duration (yrs)	6 ± 9	7 ± 7
OKS	28 ± 6	31 ± 5
PAL	1.37 ± 0.14	1.34 ± 0.09
Systolic BP (mmHg)	135 ± 12	129 ± 13
Diastolic BP (mmHg)	87 ± 10	83 ± 10

BMI = Body Mass Index; OKS = Oxford Knee Score; PAL = Physical Activity Level; BP = Blood Pressure

Table 2. Metabolic health before and after calorie restriction (CR) only or combined with aerobic exercise (CR+E).

	Calorie Restriction (n=8)		Calorie Restriction + Exercise (n=13)			
	Pre-Intervention	**Post-Intervention***	**Pre-Intervention**	**Post-Intervention***	**P value**	**Cohen's *d***
Glucose (mmol·L^{-1})	5.47 (4.93 to 6.01)	5.01 (4.46 to 5.56)	5.03 (4.66 to 5.39)	5.33 (4.90 to 5.76)	0.362	0.44
TGs (mmol·L^{-1})	1.08 (0.69 to 1.47)	1.17 (0.88 to 1.46)	1.28 (0.90 to 1.67)	0.88 (0.65 to 1.12)	0.128	0.78
TC (mmol·L^{-1})	5.36 (4.35 to 6.38)	5.25 (4.62 to 5.87)	5.53 (5.02 to 6.03)	5.10 (4.61 to 5.59)	0.696	0.19
HDL-C (mmol·L^{-1})	1.66 (1.32 to 2.00)	1.54 (1.37 to 1.71)	1.62 (1.30 to 1.95)	1.52 (1.39 to 1.65)	0.842	0.03
LDL-C (mmol·L^{-1})	3.47 (2.74 to 4.20)	3.46 (2.97 to 3.95)	3.69 (3.24 to 4.14)	3.40 (3.01 to 3.78)	0.830	0.11
NEFA (mmol·L^{-1})	0.73 (0.60 to 0.87)	0.69 (0.49 to 0.89)	0.53 (0.45 to 0.60)	0.67 (0.53 to 0.82)	0.917	0.06

TGs = Triglycerides; TC = Total Cholesterol; HDL-C = High Density Lipoprotein-Cholesterol; LDL-C = Low Density Lipoprotein-Cholesterol; NEFA = Non-Esterified Fatty Acids

*Post-intervention values are adjusted for pre-intervention values.

Data presented as mean ± 95% confidence intervals

Table 3. Body composition metrics before and after calorie restriction (CR) only or combined with aerobic exercise (CR+E).

	Calorie Restriction (n=9)		Calorie Restriction + Exercise (n=14)			
	Pre-Intervention	**Post-Intervention***	**Pre-Intervention**	**Post-Intervention***	**P value**	**Cohen's *d***
Body Mass (kg)	88.6 (78.5 to 98.8)	91.6 (90.2 to 93.0)	96.7 (86.2 to 107)	89.7 (88.6 to 90.8)	**0.043**	0.97
Waist Circumference (cm)	96.4 (89.7 to 103)	95.3 (93.2 to 97.3)	99.4 (91.7 to 107)	94.4 (92.8 to 96.1)	0.359	0.29
Waist: Hip	0.89 (0.82 to 0.96)	0.86 (0.84 to 0.88)	0.86 (0.81 to 0.92)	0.87 (0.86 to 0.88)	0.454	0.34
Fat Mass (kg)	36.3 (28.4 to 44.2)	37.3 (36.1 to 38.4)	40.8 (34.5 to 46.6)	36.8 (35.9 to 37.7)	0.570	0.26
Fat-Free Lean Mass (kg)	50.2 (44.7 to 55.7)	51.9 (50.8 to 52.9)	51.7 (45.3 to 58.1)	50.7 (49.8 to 51.5)	0.079	0.83
Body Fat (%)	40.5 (34.4 to 46.6)	40.1 (39.1 to 41.1)	42.2 (38.2 to 46.3)	40.7 (39.9 to 41.5)	0.347	0.43
Visceral Adipose Tissue (kg)	1.07 (0.809 to 1.34)	0.859 (0.745 to 0.973)	1.02 (0.837 to 1.20)	0.917 (0.826 to 1.01)	0.418	0.37

*Post-intervention values are adjusted for pre-intervention values.

Data presented as mean ± 95% confidence intervals

Table 4. Inflammatory cytokines at pre-intervention and post-intervention after calorie restriction (CR) only or combined with aerobic exercise (CR+E).

	Calorie Restriction			Calorie Restriction + Exercise				
	n	**Pre-Intervention**	**Post-Intervention***	**n**	**Pre-Intervention**	**Post-Intervention***	**P value**	**Cohen's *d***
IL-1β (pg/mL)	6	1.78 (1.35 to 2.21)	1.16 (0.29 to 2.02)	10	1.49 (0.82 to 2.16)	0.96 (0.29 to 1.62)	0.699	0.22
TNF-α (pg/mL)	8	1.82 (1.27 to 2.36)	1.55 (1.22 to 1.88)	13	1.76 (1.45 to 2.06)	1.39 (1.12 to 1.65)	0.427	0.38
IL-17a (pg/mL)	7	11.2 (7.23 to 15.2)	9.60 (8.00 to 11.2)	13	10.6 (7.85 to 13.3)	9.13 (7.96 to 10.3)	0.623	0.25
IL-18 (pg/mL)	8	505 (343 to 666)	481 (319 to 644)	13	597 (501 to 692)	419 (293 to 546)	0.544	0.29
IL-8 (pg/mL)	7	10.3 (7.43 to 13.2)	10.4 (7.01 to 13.8)	12	9.93 (6.98 to 12.9)	9.87 (7.29 to 12.5)	0.797	0.13
IL-10 (pg/mL)	7	1.08 (0.94 to 1.22)	1.10 (0.86 to 1.33)	13	0.97 (0.83 to 1.10)	1.22 (1.05 to 1.40)	0.374	0.44
IL-4 (pg/mL)	7	0.473 (0.357 to 0.589)	0.510 (0.423 to 0.598)	11	0.421 (0.291 to 0.551)	0.527 (0.457 to 0.597)	0.760	0.16
IL-13 (pg/mL)	4	4.16 (2.04 to 6.28)	9.32 (6.19 to 12.5)	3	4.65 (1.48 to 7.81)	6.41 (2.79 to 10.0)	0.170	1.67
IL-1RA (pg/mL)	4	283 (105 to 461)	305 (157 to 454)	9	220 (119 to 321)	210 (114 to 306)	0.268	0.74

*Post-intervention values are adjusted for pre-intervention values.

Data presented as mean ± 95% confidence intervals

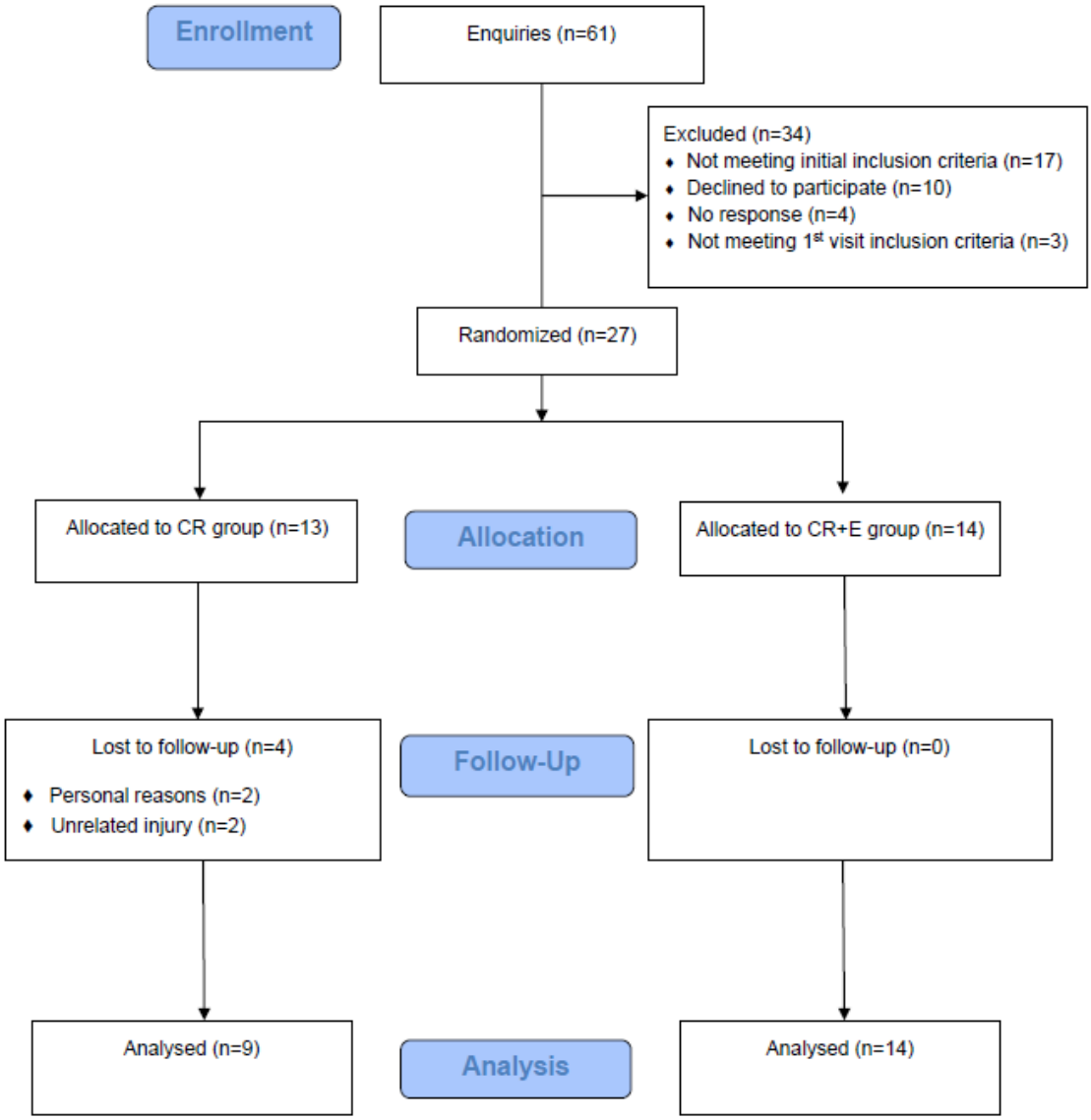
Table 5. KOOS, SF-36 and EQ-5Q subscales at pre-intervention and post-intervention after calorie restriction (CR) only or combined with aerobic exercise (CR+E).

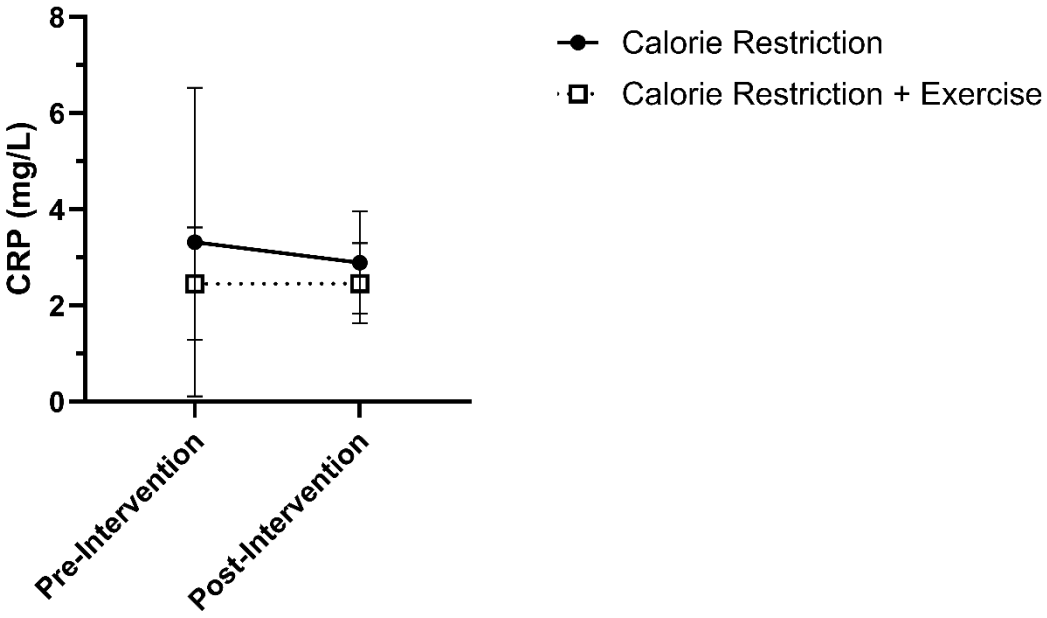
	Calorie Restriction (n=9)		Calorie Restriction + Exercise (n=14)			
	Pre-Intervention	**Post-Intervention***	**Pre-Intervention**	**Post-Intervention***	**P value**	**Cohen's *d***
KOOS						
Pain	55 (41 to 69)	61 (54 to 69)	62 (53 to 71)	73 (67 to 79)	**0.018**	1.15
Symptoms	58 (48 to 69)	58 (50 to 66)	52 (43 to 60)	68 (61 to 74)	0.066	0.87
ADL	62 (45 to 79)	69 (63 to 75)	72 (63 to 81)	81 (76 to 86)	**0.004**	1.45
Quality of Life[1]	45 (32 to 57)	42 (49 to 62)	42 (32 to 51)	58 (49 to 62)	**0.018**	1.23
SF-36[1]						
Physical Functioning	51 (26 to 75)	55 (46 to 64)	61 (50 to 72)	71 (65 to 78)	**0.007**	1.38
Physical Health	41 (4 to 78)	49 (25 to 73)	64 (42 to 87)	83 (65 to 101)	**0.029**	1.08
Emotional Problems	62 (28 to 97)	56 (37 to 74)	84 (65 to 100)	97 (83 to 111)	**0.002**	1.69
Energy/Fatigue	44 (23 to 65)	50 (41 to 60)	47 (33 to 61)	71 (64 to 78)	**0.002**	1.66
Emotional Wellbeing	70 (51 to 89)	69 (64 to 73)	80 (77 to 84)	85 (82 to 88)	**<0.001**	2.95
Social Functioning	70 (52 to 89)	77 (67 to 87)	86 (76 to 95)	88 (81 to 96)	0.072	0.87
Pain	45 (28 to 62)	55 (45 to 64)	60 (50 to 69)	68 (60 to 74)	**0.044**	0.99
General Health	56 (45 to 68)	59 (52 to 66)	59 (49 to 69)	69 (63 to 74)	**0.039**	1.02
Health Change	41 (25 to 56)	41 (38 to 65)	52 (38 to 65)	55 (44 to 65)	0.695	0.18
EQ-5D						
VAS	65 (53 to 78)	69 (63 to 75)	69 (57 to 80)	85 (80 to 90)	**<0.01**	1.97

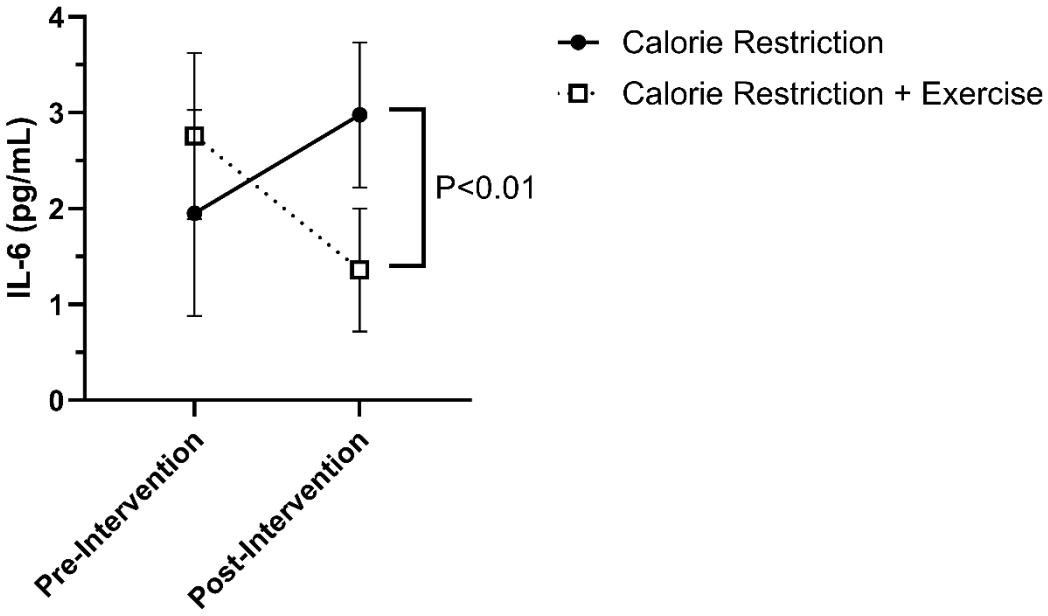
*Post-intervention values are adjusted for pre-intervention values.

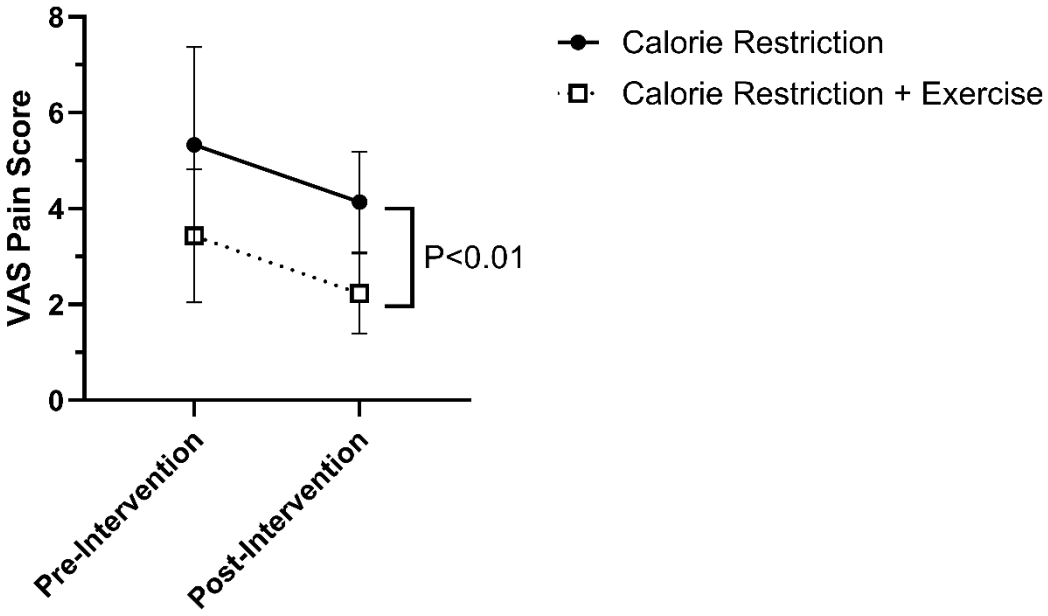
[1]CR (n=8), CR+E (n=13)

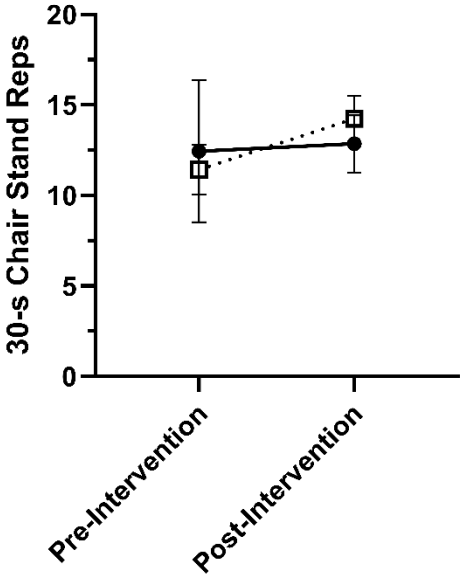
Data presented as mean ± 95% confidence intervals

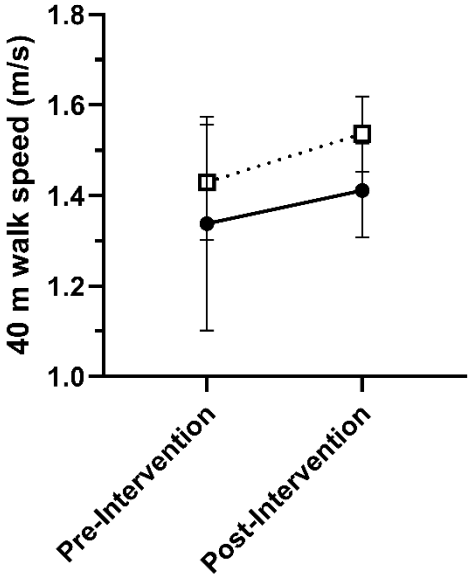

Enrollment
Enquiries (n=61)
Excluded (n=34)
Not meeting initial inclusion criteria (n=17)
Declined to participate (n=10)
No response (n=4)
Not meeting 1st visit inclusion criteria (n=3)
Randomized (n=27)
Allocated to CR group (n=13)
Allocation
Allocated to CR+E group (n=14)
Lost to follow-up (n=4)
Personal reasons (n=2)
Unrelated injury (n=2)
Follow-Up
Lost to follow-up (n=0)
Analysed (n=9)
Analysis
Analysed (n=14)

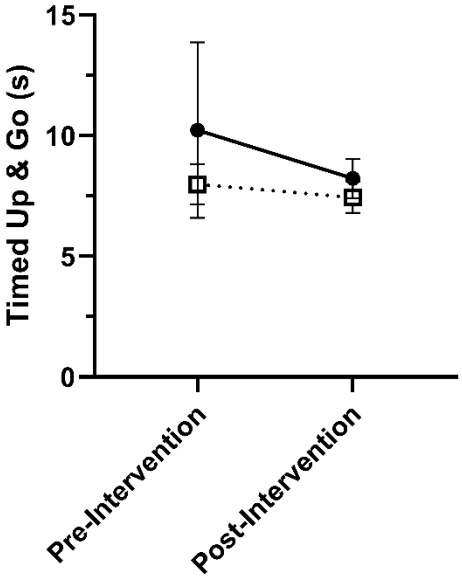

8
6
4
2
0
CRP (mg/L)
Pre-Intervention
Post-Intervention
Calorie Restriction
Calorie Restriction + Exercise

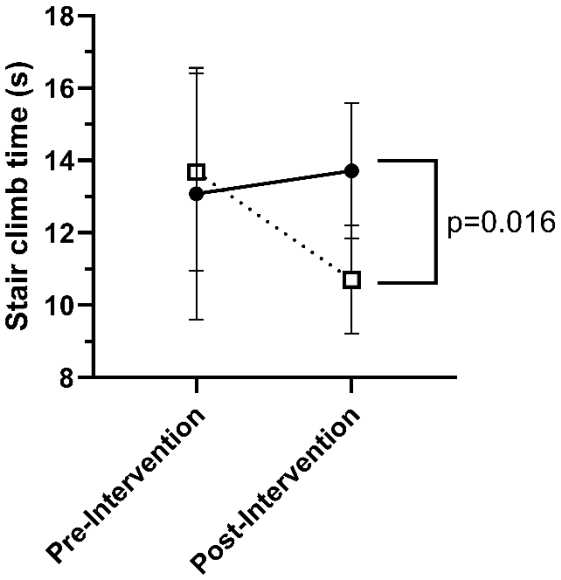

4
3
2
1
0
IL-6 (pg/mL)
P<0.01
Pre-Intervention
Post-Intervention
Calorie Restriction
Calorie Restriction + Exercise


VAS Pain Score
8
6
4
2
0
P<0.01
Pre-Intervention
Post-Intervention
Calorie Restriction
Calorie Restriction + Exercise


30-s Chair Stand Reps
20
15
10
5
0
Pre-Intervention
Post-Intervention


40 m walk speed (m/s)
1.8
1.6
1.4
1.2
1.0
Pre-Intervention
Post-Intervention


Timed Up & Go (s)
15
10
5
0
Pre-Intervention
Post-Intervention


Stair climb time (s)
18
16
14
12
10
8
p=0.016
Pre-Intervention
Post-Intervention